BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

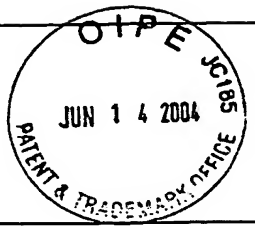
Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

IFW



U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL OF PRIORITY DOCUMENT	Docket Number: 12895/46001	Confirmation No.:

Application Number	Filing Date	Examiner	Art Unit
10/781,997	February 19, 2004	Not Yet Assigned	1615

Invention Title	Inventor
ANTIFUNGAL ORAL DOSAGE FORMS AND THE METHODS FOR PREPARATION	KRISHNAN et al.

Address to:

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:
Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
on June 11, 2004
Date: June 11, 2004 Reg. No. 52,162
Signature: John Resek

SIR:

A claim to the Convention Priority Date pursuant to 35 U.S.C. § 119 of Application No. 1231/mum/2003, filed 28 November 2003 in India was previously made. To complete the claim to the Convention Priority Date, a certified copy of the priority application is attached.

If any fees are necessary they may be charged to Deposit Account 11–0600.

Dated: June 11, 2004

By: John Resek
John F. Resek Reg. No. 52,162

KENYON & KENYON
One Broadway
New York, N.Y. 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)
Customer No. 26646

INTELLECTUAL
PROPERTY **INDIA**
PATENTS / DESIGNS / TRADE MARKS/
GEOGRAPHICALINDICATIONS

सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 28/11/2003 in respect of Patent Application No. 1231/MUM/2003 of Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No. 26511, Mumbai – 400 026, INDIA.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 17th day of march 2004.

(N.K.GARG)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1
THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF A PATENT (Section 5(2)7 and Rule 33A)

We, Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026 INDIA hereby declare

1(a) that we are in possession of an invention titled **"ITRACONAZOLE ORAL DOSAGE FORMS."**

(b) that the provisional specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are

(a) **NILENDU SEN, SHRIKANT BHONSLE, ANANDI KRISHNAN** All citizens & residents of India belonging to Glenmark Pharmaceuticals Limited , B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026

(b) **KAVITA CHANDURKAR** citizen of India & resident of Apartment C-301, Janeway Apartment , New Foundland Drive, St John's NL A1A1T1, Canada.

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Glenmark Pharmaceuticals Limited
Plot No.A-607, T.T.C Industrial Area
M.I.D.C., Mahape
Navi Mumbai – 400 709
INDIA

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

WTO-88
1231
5750

(Signed) _____
NILENDU SEN

(Signed) _____
KAVITA CHANDURKAR

(Signed) _____
SHRIKANT BHONSLE

(Signed) _____
ANANDI KRISHNAN

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. Following are the attachments with the application
(a) Provisional Specification (16 pages, in duplicate)
(b) Fee Rs. 3000.00 (three thousand rupees only) by Cheque No.054922 dated Nov 27, 2003 drawn on UTI Bank Ltd

We request that a patent may be granted to us for the said invention

Dated this Twenty Eighth (28th) day of November 2003

CHERYL PINTO
Director
Glenmark Pharmaceuticals Limited

Received Rs. 3000/- in Cash
Cheque/M.O./P.O. on 28/11/03
Vide Entry No. 5750 in the Register of Valuables, Bombay.

To,
The Controller of Patents
The Patents Office Branch, Mumbai

BS/MUM-WTO/2003
1231/MUM/2003
Dt: 28/11/03

FORM 2

THE PATENTS ACT 1970
(Act 39 of 1970)

PROVISIONAL SPECIFICATION

(SECTION 10)

ITRACONAZOLE ORAL DOSAGE FORMS

Glenmark Pharmaceuticals Limited, an Indian Company,
registered under the Indian company's Act 1957 and
having its registered office at

B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road
Post Box No. 26511
Mumbai - 400 026, India

THE FOLLOWING SPECIFICATION DESCRIBES THE NATURE OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to novel dosage forms of itraconazole which may be manufactured on industrial scale using convenient processing techniques well known to those skilled in the art in order to obtain formulations suitable for oral administration which enhance the solubility of the drug wherein the techniques used for solubilization of the said drug are novel.

BACKGROUND OF THE INVENTION

The present invention is concerned with a novel composition of antifungal agents which have low solubility in aqueous media, a process for preparing said composition and pharmaceutical dosage forms for oral administration comprising said novel composition.

The development of efficacious pharmaceutical compositions of azole antifungals such as for example, itraconazole is hampered considerably by the fact that said antifungals are only very sparingly soluble in water.

Itraconazole is a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs),each possessing three chiral centers. It may be represented by the following structural formula and nomenclature:

(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy] phenyl]-1-piperazinyl]phenyl]-Ä2-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Ä 2-1,2,4-triazolin-5-one or (±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Ä 2-1,2,4-triazolin-5-one.

Itraconazole has a molecular formula of C35H38Cl2N8O4 and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on

extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

The following prior art review reveal various techniques to obtain orally administrable dosage forms of itraconazole. All of these suffer form the disadvantages which have been mentioned in the review necessitating the current invention.

US patent No: 5633015 [Assignee: Not mentioned but listed as a Janssen product in the Orange Book Filed: March 13, 1995; Issued: May 27, 1997] relates to novel compositions of antifungals which have a low solubility in aqueous media. The process that is described in this patent involves the use of hazardous solvents and is extremely time consuming. As per the claims and the detailed description of this invention the shape of the cores and the size are critical to obtaining a dosage form with good availability on oral administration. Our invention overcomes these limitations.

US 5707975 {Assignee: Janssen Pharmaceutica N.V.; Filed: February 22, 1996; Issued : January13, 1998] The invention relates to formulations for oral administration which comprise an antifungal, e.g. itraconazole or saperconazole, as active ingredient, a sufficient amount of a cyclodextrin or a derivative thereof as a solubilizer, an aqueous acidic medium as bulk liquid carrier and an alcoholic co-solvent. The pharmaceutical dosage form comprises a minimal volume of air above the solution, preferably an inert gas such as nitrogen since oxidative degradation may occur on storage. Besides the exclusion of air (oxygen), storage at temperatures below 25.degree. C. also beneficially affects the maximum shelf life of the formulation for oral administration. Liquid dosage forms are considered to be less stable in general when compared to solid dosage forms for oral administration and may also have shorter shelf lives. This invention therefore suffers form the disadvantage of possible instability of the dosage from.

US 6039981 [Assignee: Hanmi Pharma Co. Ltd. ; Filed October 4, 1999; Issued: March 21, 2000] claims a fused mixture of itraconazole and phosphoric acid. The process involves

heating the mix to a temperature of 100 to 170 °C. However, the manufacturing process of the solid dispersion is hampered by a number of difficulties in controlling various process variables. On a large scale this process may be difficult to manufacture.

US 6365188 [Assignee: Janssen Pharmaceutica ; Filed: May 20, 1998 Issued: April 02, 2002] The present invention involves a process for preparing solid mixtures by melt-extrusion comprising one or more active ingredients, preferably one or more practically insoluble active ingredients and one or more cyclodextrins to about 240°C. The invention further concerns pharmaceutical compositions comprising the above mixture. However, the manufacturing process of the solid dispersion is hampered by a number of difficulties in controlling various process variables. On a large scale this process may be difficult to manufacture.

US 6509038 [Assigned: Janssen Pharmaceutica N.V. Filed: Nov 19, 1998 Issued: January 21, 2003] teaches a solid dispersion of itraconazole in a water-soluble polymer, which is prepared by subjecting a mixture of itraconazole and the water-soluble polymer to a melt-extrusion process at a temperature ranging from 245°C to 265°C. This solid dispersion is described to have an improved bioavailability of itraconazole which is not influenced by ingested foods. However, the manufacturing process of the solid dispersion is hampered by a number of difficulties in controlling various process variables. On a large scale this process may be difficult to manufacture.

US 6346533 [Assigned: Dong-A Pharmaceutical Company; Filed: Dec. 14, 1999; Issued: Feb. 12, 2002] a novel means of providing improved solubility of itraconazole by reducing particle size and changing the crystallinity of itraconazole from crystalline to amorphous by means of dissolution induced drying. As per this invention itraconazole is dissolved in methylene chloride which is well known in prior art as a good solvent of itraconazole [US 5633015]. Also the particle size of itraconazole is maintained at 0.5 microns to 10 microns which is also well known in the prior art [WO 98/00116] though different means of achieving this particle size are mentioned. The disadvantage of this patent is that the processing techniques used in this invention involve the use of methylene chloride which is

a hazardous solvent and is well known as a carcinogen. Also no in vivo bioavailability data or comparison with the marketed product is revealed.

WO 01/85135 {Assignee: Dong-A Pharma; Filed: 20th April 2001; Published: 15th November, 2001] Teaches a process in which itraconazole and a water soluble pH independent polymer are dissolved in a combination of solvents like methylene chloride , chloroform, ethanol or methanol and then spray dried to obtain fine particles which are then compressed into suitable dosage forms. This disadvantage of this process is that large quantities of potentially hazardous solvents are involved and may be a health hazard.

US 2002 01/ 0150620 [Assignee: Not Mentioned; Filed: August 20, 2001; Published: 17 October, 2002] reveals a process for formulation of itraconazole dosage forms wherein essentially the itraconazole and the water soluble film forming polymer are dissolved in an acidified ethanolic solution and this solution is sprayed onto beads to obtain cores having a coating film comprising a water soluble polymer and itraconazole. In this invention the molar concentration of acid used is in the range of 1 to 3 moles and the coating solution is an 8% w/w solution. This results in very long processing times and may be commercially unviable. Our invention is able to achieve solubility without using the water soluble film forming polymer which according to this invention is an essential component.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel means of solubilization of itraconazole which is a well known antifungal agent. The processing techniques described in this invention aid in the manufacture of orally administrable dosage forms of itraconazole.

The prior art detailed above reveals that prior to this invention the known means of solubilization of itraconazole in order to obtain bioavailable dosage forms were as detailed below:

1. Itraconazole when solubilized along with hydroxy propyl methylcellulose [HPMC] in a non-aqueous solvent mix of methylene chloride and ethanol and sprayed on beads of specific size yields a bio available dosage form. According to this patent the solubilization of itraconazole in the presence of hydrophilic polymers which can coat the cores and form a film are essential. Our invention circumvents the use of such hydrophilic film forming polymers. [US 5633015]

2. Itraconazole when solubilized using a mixture of ethanol and acid in the presence of hydrophilic film forming polymers like HPMC and sprayed on beads yields a bio available dosage form. According to this invention the presence of hydrophilic film forming polymers are essential to aid the solubility and enhance the dissolution / bioavailability. Our invention circumvents the use of such hydrophilic film forming polymers.[WO 02/062318]

3. Itraconazole when heated with HPMC or Phosphoric acid or beta-cyclodextrin and melt extruded at very high temperatures yields a solid dispersion which is claimed to have enhanced bioavailability. The melting of itraconazole along with the mentioned excipients is essential to achieving the desired solubility/ bioavailability. Our invention does not involve the use of high temperatures which may be detrimental to the stability of the product and also details a very convenient processing technique.[US 6509038, US 6039981 and US 6365188]

4. Itraconazole when dissolved in methylene chloride and spray dried or fluid bed granulated or centrifugally granulated under controlled drying conditions yields amorphous forms of itraconazole which are claimed to have a better bioavailability. The Organic volatile impurities [OVI] limits for methylene chloride are extremely stringent and extensive heating and drying steps are essential to bring down the limits of methylene chloride to recommended levels. Methylene chloride is known to be a health hazard .The liver and skin is also susceptible to acute effects from methylene chloride exposure. Chlorinated hydrocarbons as a class (of which methylene chloride is a member) are

generally toxic to the liver. Our invention does not use any of the solvents which could pose as health hazards. [US 6346533]

5. Itraconazole when dissolved with a water soluble pH-independent polymer using non-aqueous solvents like methylene chloride, chloroform ethanol or methanol and spray-dried yields itraconazole that shows more improved bioavailability and in-vivo absorption while retaining its therapeutic effect over the wide gastric pH range. According to this invention the presence of a pH-independent water-soluble polymer[s] is essential to aid the solubility and enhance the dissolution / bioavailability, when used in the range of 10 to 1000 part by weight based on itraconazole. Our invention circumvents the use of such water soluble pH independent polymers.

As per the novel processes used in this invention all of the above mentioned disadvantages are overcome. The following strategies detail the quantitative formula and process for manufacture of itraconazole dosage forms which have an in vitro dissolution which is comparable with the marketed product Sporanox®.

Example 1

The following Table lists the formula used in Example 1

Table 1: Quantitative Formula

S.No:	Ingredients	Quantity per dose [mg]	% w/w
1.	Itraconazole	100	21.74
2.	Mannitol	302	65.65
3.	Croscarmellose sodium	46.0	10.0
4.	Polyvinyl pyrrolidone K 25	12.0	2.60
5.	Conc. Hydrochloric acid [37 %]	0.0415 ml [0.04897 g 48.97 mg]	Molar ratio to drug **1:3.5** moles
6.	Ethanol*	-	-
7.	Purified Water*	-	-
	Total	**460.0**	

*Does not appear in final product.

Molar ratio Calculations:

Molecular weight of Itraconazole is 706 and that of Hydrochloric acid is 36.5.

Therefore as per the quantities used the molar ratio of antifungal agent: HCl is calculated to be 1:3.5 moles.

The following paragraphs enumerate the role played by each of the components that comprise the said invention.

Itraconazole: This is the antifungal agent. Micronized API having a particle size distribution of 95% below 10 microns has been used. This limit is set in order to have uniformity in the API lots. Also the micronized API will dissolve faster in the ethanolic acid medium.

Mannitol: Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. [Handbook of Pharmaceutical Excipients, Third Edition] It is a water soluble monomer having no film forming properties. It is used as a sweetening agent and a diluent in tablets and capsules. In the present invention it is used as a base bulking agent and solubility enhancer for itraconazole

Croscarmellose sodium: Croscarmellose sodium is a cross linked polymer of carboxymethyl cellulose sodium. [Handbook of Pharmaceutical Excipients, Third Edition] It is a hydrophilic water insoluble polymer which used in pharmaceutical preparations as a disintegrant and has no film forming properties. In the present invention its role is in providing disintegration of the granules formed.

Polyvinyl pyrrolidone (PVP): Polyvinyl pyrrolidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidone groups, the degree of polymerization of which results in polymers of various molecular weights. The PVP K-25 has a molecular weight of 30000 units. [Handbook of Pharmaceutical Excipients, Third Edition]

As per the claims of **US 5633015** the ratio of antifungal agent: hydrophilic polymer should be in the range of 1:1 to 1:2 in order to have a coating film of the hydrophilic polymer. Also it is essential to incorporate the antifungal agent in the hydrophilic polymer and apply the mixture as a coat over small beads. Although PVP K-25 may be considered as a hydrophilic polymer, in the present invention the w/w ratio of antifungal agent: polymer PVP K 25 is 1:0.12 [10:1.2] and at this level the role played is not that of a film forming agent or solubility enhancer. Rather its role is a binding agent in the formation of granules.

As per the claims of US patent application **US 2002 01/50620** the percentage weight by weight compositions consists of 5 to 40 percent of itraconazole and 10 to 80 percent of water soluble polymer selected from the group consisting of Hydroxy propyl methyl cellulose, Methacrylate, Hydroxy propyl cellulose and polyvinylpyrrolidones. This water soluble polymer is used as a coating agent and forms a film along with itraconazole. In our invention the % weight by weight of itraconazole is 21.74 % and that of the hydrophilic

water soluble polymer is 2.6 % weight by weight. At these concentrations no film forming properties can be attributed to the polymer. Rather its role is a binding agent in the formation of granules.

As per the claims of patent number **US 6509038** the essential composition comprises of itraconazole and one or more pharmaceutically acceptable water soluble polymers in the w/w ratio of 21.65 % itraconazole and 32.48 % HPMC 2910 5 mPas. In the present invention the water soluble polymer used is PVP K 25 at the weight by weight ratio of 21.74 % itraconazole and 2.6 % PVP K 25. At these concentrations no film forming properties can be attributed to the polymer. Rather its role is a binding agent in the formation of granules.

Concentrated hydrochloric acid : [HCl] Hydrochloric acid occurs as a clear colourless, fuming aqueous solution of hydrogen chloride with a pungent odour. Its functional category is as an acidifying agent. [Handbook of Pharmaceutical Excipients, Third Edition]. The antifungal agent is not soluble in hydrochloric acid alone.

Ethanol: Ethanol is used as a solvent in pharmaceutical formulations. [Handbook of Pharmaceutical Excipients, Third Edition]. The antifungal agent itraconazole is poorly soluble in ethanol. At the concentrations used in the current invention this quantity alone is insufficient to dissolve the drug. The use of acidified ethanol is essential to solubilise the drug.

Role of ethanolic acid:

As per the claims of US patent application No: **US 2002 01/50620** the essential components involve use of itraconazole a water soluble polymer ethanol and acid as stated in the main claims

1. "A method of manufacturing an itraconazole oral dosage form that is substantially free of residual methylene chloride, said method comprising the steps of: providing a working solution consisting ***essentially of an alcohol, a strong acid, itraconazole, a water-soluble polymer, and water,*** *with said itraconazole and said strong acid present in said working*

solution in a ratio of 1 Mole itraconazole to from 1 to 3 Moles strong acid, and with said strong acid selected from the group consisting of inorganic acids and organic sulphonic acids; providing particles formed from a pharmaceutically acceptable core material; combining said working solution with said particles to produce itraconazole-coated particles; drying said itraconazole-coated particles; and forming said dried itraconazole-coated particles into an itraconazole oral dosage form that is substantially free of residual methylene chloride."

11. "A pharmaceutically acceptable particle comprising: a central rounded or spherical core comprised of a core material; and a coating film formed on said core, said coating film comprising a water-soluble polymer and itraconazole; with said particle comprising, by weight, from 5 to 40 percent itraconazole; from 10 to 50 percent particle core material; and from 10 to 80 percent water-soluble polymer; and with said particle containing less than 200 ppm methylene chloride."

The present invention uses ethanolic acid to dissolve the itraconazole but does not use the water soluble polymer as an essential component at the above mentioned weight ratio of 10 to 80 percent of the final composition. Also the novel means of obtaining the dissolution of itraconazole involves the use of a water soluble monomer i.e. mannitol in the weight ratio of 65.65 % of the final composition.

Brief Process of the Invention:

1. Itraconazole is dissolved in the mixture of ethanol, concentrated hydrochloric acid (37%) and purified water.
2. Mannitol, croscarmellose sodium and the binding agent poly vinyl pyrrolidone K-25 are added together and mixed well.
3. The ingredients of step2 are mixed well and then granulated by the solution of step1 by top spray technique using a fluid bed granulator.
4. The granules thus obtained can be directly filled into capsules or can be compressed into tablets.

Example 2

The following Tablet lists the formula used in Example 2

Table 2: Quantitative Formula

S.No:	Ingredients	Quantity per dose [mg]	% w/w
1.	Itraconazole	100	21.74
2.	Microcrystalline Cellulose	302	65.65
3.	Croscarmellose sodium	46.0	10.0
4.	Polyvinyl pyrrolidone K 25	12.0	2.60
5.	Conc. Hydrochloric acid [37 %]	0.0415 ml [0.04897 g 48.97 mg]	Molar ratio to drug **1:3.5** moles
6.	Ethanol*	-	-
7.	Purified Water*	-	-
	Total	**460.0**	

*Does not appear in final product.

The following paragraphs enumerate the **role played by Microcrystalline Cellulose** that comprises the said invention along with other ingredients as mentioned in Strategy 1.

Microcrystalline Cellulose: Microcrystalline Cellulose is purified, partially depolymerised cellulose. [Handbook of Pharmaceutical Excipients,Third Edition]. It is a hydrophilic water insoluble polymer and has no film forming properties. In the present invention its role is in providing carrier/bulking agent for the active ingredient.

Brief Process of the Invention:

1. Itraconazole is dissolved in the mixture of ethanol, concentrated hydrochloric acid (37%) and purified water.
2. Microcrystalline Cellulose, croscarmellose sodium and the binding agent poly vinyl pyrrolidone K-25 are added together and mixed well.
3. The ingredients of step2 are mixed well and then granulated by the solution of step1 by top spray technique using a fluid bed granulator.
4. The granules thus obtained can be directly filled into capsules or can be compressed into tablets.

Example 3

The following Tablet lists the formula used in Example 3

Table 3: Quantitative Formula

S.No:	**Ingredients**	**Quantity per dose [mg]**	**% w/w**
1.	Itraconazole	100.0	20.39
2.	Microcrystalline Cellulose	135.0	27.53
3.	Croscarmellose sodium/Crospovidone	46.0	9.38
4.	Hydroxypropyl-β-cyclodextrin	167.0	34.05 (Molar ratio to drug **1:0.9** moles)#
5.	Polyvinyl pyrrolidone K 25	12.0	2.45
6.	Crospovidone	28.1	5.73
7.	Conc. Hydrochloric acid [37 %]	0.0415 ml [48.97 mg]	Molar ratio to drug **1:3.5** moles
8.	Ethanol*	-	-
9.	Purified Water*	-	-
	Total	**490.4**	

#Molecular Weight of HP3-β-CD used is 1309

*Does not appear in final product.

The following paragraphs enumerate the role played by Hydroxypropyl-β-cyclodextrin that comprises the said invention along with other ingredients as mentioned in Strategy 2.

Hydroxypropyl-β-cyclodextrin: Hydroxypropyl-β-cyclodextrin belongs to the class of cyclodextrins which are cyclic oligosaccharides containing at least 6 D-(+)-glucopyranose units attached by α (1→4) glucoside bonds. The β- cyclodextrin contains 7 glucose units. [Handbook of Pharmaceutical Excipients, Third Edition]. As per definition polymers are large molecules consisting of repeated chemical units ('mers') joined together, usually in a line, like beads on a string. Each 'mer' is typically made up of more than 5 and less than 500 atoms; the word 'polymer' is applied when there are more than about 500 'mers' stuck together. Polymeric molecules do not have well defined molecular weights. HP3-β-CD used herein has a molecular weight of 1309. Thus cyclodextrins can not be classified as polymers and does not have film forming properties.

Hydroxypropyl-β-cyclodextrin has been mentioned as an agent for solubilizing itraconazole US Patent 5707975, but no techniques for incorporating the same in oral solids are mentioned. Also the concentration used in the solution as per the above claim contains 1g of itraconazole to 40g of Hydroxypropyl-β-cyclodextrin per 100ml of the solution which is extremely high as compared to the amount used in the present invention to be incorporated in the solution of itraconazole which when sprayed on excipients in a fluid bed processor yield itraconazole formulation with superior dissolution.

Also as per US Patent 6365188 both itraconazole and hydroxypropyl-β-cyclodextrin has to be heated together and subjected to melt extrusion to form a suitable bioavailable dosage form. There are no reported prior art which describes the processing technique for incorporation of hydroxypropyl-β-cyclodextrin as described in the present invention.

Brief Process of the Invention:

1. Itraconazole is dissolved in the mixture of ethanol, concentrated hydrochloric acid (37%) and purified water.
2. Hydroxypropyl-β-cyclodextrin is dissolved in sufficient volume of purified water.
3. The solution of step1 & step2 are mixed together and stirred well.
4. Microcrystalline Cellulose, croscarmellose sodium/crospovidone and the binding agent poly vinyl pyrrolidone K-25 are added together and mixed well.
5. The ingredients of step4 are mixed well and then granulated by the solution of step3 by top spray technique using a fluid bed granulator.
6. Crospovidone & Magnesium stearate are added together to the granules and then roll compacted.
7. The roll compacted mass is then sized/milled.
8. Crospovidone is then added to the granules from step 7.
9. The granules are then filled into capsules.

In Vitro Dissolution Profile comparison with Sporanox®

The comparative in-vitro dissolution Profiles of the products of Example 1, Example 2 & Example 3 and that of Sporanox® (Janssen) are given below.

Apparatus: USP Type 2

RPM: 100

Medium: 900ml of Simulated Gastric Fluid (SGF) without enzymes at 37°C

Table 4: Comparative Dissolution Profile

Time (min)	% Itraconazole dissolved			
	Sporanox (B.No. 2JG256)	Example 1	Example 2	Example 3
15	27	4	42	55
30	48	28	62	83
45	66	49	73	89
60	79	61	77	93

Dated this Twenty Eighth (28th) **day of** November **2003**

CHERYL PINTO
Director
Glenmark Pharmaceuticals Limited